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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/762,587	09/06/2001	Antonio Grillo-Lopez	27693-01186	5272

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SIDLEY AUSTIN LLP
ATTN: DC PATENT DOCKETING
1501 K STREET, NW
WASHINGTON, DC 20005

EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	**PAPER NUMBER**
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/762,587	GRILLO-LOPEZ, ANTONIO	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 7 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 7 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claim 7 is being examined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 7 remains rejected under 35 USC 103, as being obvious over Maloney et al, in view of Press et al, Kaminsky et al, 1996, and Kaminsky et al (US 6,287,537, filed 05/29/1998), and further in view of Wahl et al, for reasons already of record in paper of 07/03/06.

The response asserts that the Office has not presented evidence that establishes that the term "refractory," as used in the claim, has the broad meaning alleged in the rejection. The response assert that for the reasons argued at length previously, applicant maintains that the examiner has not presented evidence that demonstrates that "refractory," a term of art in clinical oncology, would have been understood by one of skill as the equivalent of "nonresponsive," as the Office holds.

The response has been considered but is not found to be persuasive for the following reasons:

Since "refractory" encompasses "not responsive to treatment" as defined in Webster's II Dictionary, 1994, page 988, and since the meaning of "refractory" is not clear in the specification, the subject refractory to treatment with non-radiolabeled rituximab in the claimed method is reasonably interpreted as encompassing any subject having CD20-positive cell lymphoma, wherein the subject is resistant or not responsive to said treatment, as manifested by not showing anti-tumor response. The refractory subject is clearly the same as the 54% of NHL patients in the reference by Maloney et al, which patients express CD20 antigen, but do not respond to the treatment with the non-radiolabeled anti-CD20 antibody.

The response asserts that the cited prior art does not set forth as evidence of motivation and a reasonable expectation of success. In particular, none of the cited references teaches that a radiolabeled anti-CD20 antibody would be expected to be efficacious to treat a B-cell lymphoma patient refractory to any unlabeled anti-CD20 antibody, as the Office appears to believe.

The response has been considered but is not found to be persuasive for the following reasons:

One would have been motivated to treat those population of patients who express CD20 antigen, but who do not respond to the treatment with the non-radiolabeled anti-CD20 antibody, taught by Maloney et al, with radiolabeled anti-CD20, in view of Kaminsky et al (US 6,287,537), which teach that: 1) the radiolabeled anti-CD20 is effective in those cases wherein the patients do not respond to non-radiolabeled anti-CD20 alone (column 21, third paragraph, lines 48-54),

and 2) the anti-tumor response of the non-radiolabeled antibody alone is only seen after a large dose of the non-radiolabeled antibody (column 21, lines 40-54), thus clearly suggesting that although the non-radiolabeled anti-CD20 antibody has some anti-tumor effect, it is not efficient, because a large amount of it is required to show its effect.

Further, one would have a reasonable expectation of success, in view of: 1) the above teaching of Kaminsky et al that the radiolabeled anti-CD20 is effective in those cases wherein the patients do not respond to non-radiolabeled anti-CD20 alone, and 2) the teaching of Press et al that iodine-131 anti-CD20 antibody is successfully used for patients with B-lymphoma, and the teaching of Wahl et al that iodine-131 anti-CD20 antibody is also safely used for patients with B-lymphoma that are previously treated with the lableled antii-CD20 antibody, but are relapsed.

The response asserts that the primary reference, Maloney, does not discuss treatment options for non-Hodgkin's lymphoma (NHL) patients who fail to respond to the administration of rituximab. The response asserts that whether or not such patients are "refractory" to rituximab, as the Office asserts, Maloney teaches nothing more than their lack of response to the chimeric anti-CD20 antibody therapy. The response asserts that the reference is silent as to any other therapy that might be attempted.

The response has been considered but is not found to be persuasive for the following reasons:

The response argues individual reference, instead of a combination of references. Although Maloney et al do not teach treatment options for non-Hodgkin's lymphoma (NHL)

patients who fail to respond to the administration of rituximab, an anti-CD20 antibody, this is compensated by the teaching of Kaminsky et al. That is, one would have been motivated to treat those population of patients with radiolabeled anti-CD20, in view of Kaminsky et al (US 6,287,537), which teach that: 1) the **radiolabeled** anti-CD20 is **effective** in those cases wherein the patients **do not respond** to non-radiolabeled anti-CD20 alone (column 21, third paragraph, lines 48-54), and 2) the anti-tumor response of the non-radiolabeled antibody alone is only seen after a large dose of the non-radiolabeled antibody (column 21, lines 40-54), thus clearly suggesting that although the non-radiolabeled anti-CD20 antibody has some anti-tumor effect, it is not efficient, because a large amount of it is required to show its effect.

The response asserts that Wahl abstract does not appear to relate to the subject matter of the claim. The response asserts that while it describes the administration of a second course of [I-131]- anti-B 1 radioimmunotherapy to NHL patients, it is silent about whether any of the treated patients were refractory to prior therapy using an unlabeled antibody.

The response has been considered but is not found to be persuasive for the following reasons:

The response argues individual reference, instead of a combination of references. The Wahl reference shows that [I-131]- anti-B 1 radioimmunotherapy to NHL patients is effective and safe, even with its prior usage. Thus, in view of the teaching of Kaminsky et al, Press et al, and Wahl, one would have motivated with a reasonable expectation of success to use radiolabled anti-CD20 antibody for those patients who do not response to anti-CD20 antibody taught by Maloney et al, supra.

The response further asserts as follows:

Neither of the two Kaminski references identifies or discusses any patient that fails to respond to a therapeutic dosage of unlabeled antibody. Every patient described in the JCO paper and in the '537 patent was treated with the complete "pre-dosing"-plus-radiotherapy regimen. Neither reference describes a control involving the treatment of an evaluable patient with only unlabeled antibody.

The response has been considered but is not found to be persuasive for the following reasons:

Contrary to the response assertion, the passage "in these cases and those in which a response appeared to occur **only after** an RIT (radiolabeled anti-CD20 antibody) dose, a targeted radiation effect is also likely" (Kaminsky et al, column 21, lines 48-50) indicates that the radiolabeled anti-CD20 is effective in those cases wherein the patients do not respond to **non-radiolabeled anti-CD20** treatment**, prior to** treatment with radiolabeled anti-CD20. Which patients clearly were treated with only unlabeled antibody before the treatment with radiolabeled anti-CD20 antibody. Further, Kaminsky et al teach that the anti-tumor response of the non-radiolabeled antibody is only seen after a large dose of the non-radiolabeled antibody (column 21, lines 40-54). It is noted that the treatment taught by Kaminsky et al involves a first treatment with non-labeled anti-CD20 antibody, and after 0-4 weeks, followed by a second treatment by 131-I labeled anti-CD20 antibody.

The response asserts as follows:

Furthermore, neither reference reports on any patient given a full "pre-dosing" quantity of unlabeled antibody in advance of a radiotherapeutic dose of [131-I]-anti-B1 by as long as the interval that the authors/applicants allowed for assessing a clinical response to radiotherapy. Thus, neither reference examines whether any patient responded or failed to respond to any effective dose of unlabeled anti-B1. Neither Kaminski reference provides evidence of motivation to treat the specific population of patients required by the claim, because neither identifies or discusses such a population. The passage in the '587 patent at col. 21, lines 48-54 does not allow one of skill to conclude whether or not any of the reported patients would have failed to respond to the administration of unlabeled antibody alone. The cited passage teaches that the full benefit of the regimen is observed only after radioimmunotherapy (RIT), not that any of the patients were demonstrated to be refractory to unlabeled antibody. This is particularly so in as much as the protocol to which the cited passage relates involves administration of unlabeled antibody with a tracer dose of radiolabel over **a period of 0 to 4 weeks** ('587 at col. 14, lines 5-12), followed by a therapeutic dose of radiolabeled antibody in a timeframe only described as "[a]t least one week after the last trace-labeled dose" (col. 14, line 13). In contrast, clinical responses to the radiotherapy regimen is evaluated "4 to 6 weeks post RIT, and every two to three months thereafter" (col. 16, lines 8-9). The cited passage does not allow one of skill to conclude whether or not any of the reported patients would have failed to respond to the administration of unlabeled antibody alone.

The response has been considered but is not found to be persuasive for the following reasons:

The response has not provided any evidence showing that: 1) the evaluation of the response to unlabeled anti-CD20 antibody by Kaminsky et al, and 2) the 0-4 week time period for evaluating the response to non-labeled anti-CD20 antibody is not valid. The response has not provided any evidence showing that the doses of the unlabeled anti-CD20 antibody taught by Kaminsky et al are not effective. Further, although the unlabeled anti-CD20 antibody is effective in some cases (Kaminsky et al, column 21, lines 30-48), however, in those cases where the patients do not response to the prior treatment with unlabeled anti-CD20 antibody, the treatment with radiolabled anti-CD20 antibody is effective, as clearly indicated by the following passage in Kaminsky et al "in these cases and those in which a response appeared to occur **only after** an RIT (radiolabeled anti-CD20 antibody) dose, a targeted radiation effect is also likely" (column 21, lines 48-50).

The response asserts as follows:

Moreover, the logic of the Office's argument cuts against the teachings of the Kaminski references. If one of ordinary skill considered that a given patient was refractory to an unlabeled antibody, that patient would not be treated with any additional unlabeled antibody since the treatment would be expected to be without effect. Yet Kaminski teaches that "pre-dosing" with unlabeled antibody contributes to the effectiveness of the radioimmunotherapy protocol described in the references. Neither Kaminski reference provides motivation to omit part of the therapeutic protocol it sets forth.

The response has been considered but is not found to be persuasive for the following reasons:

Although Kaminski teaches that "pre-dosing" with unlabeled antibody contributes to the effectiveness of the radioimmunotherapy protocol in certain cases or certain conditions (the anti-tumor effect of the antibody moiety), Kaminsky et al also teach that "in those cases in which a response appeared to occur **only after** an RIT dose (therapy with radiolabeled anti-CD20 antibody), a targeted radiation effect is also likely" (column 21, lines 48-50), i.e. for those who do not response to the pretreatment with non-radiolabeled antibody, the treatment with radiolabeled anti-CD20 is effective. Thus the teaching of Kaminsky et al provides motivation for treating those who do not respond to the unlabeled anti-CD-20 antibody alone (those in which a response appeared to occur **only after** an RIT), because the radio-labeled anti-CD20 antibody treatment is effective in those cases.

NEW REJECTION BASED ON NEW CONSIDERATION

Double Patenting

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Claim 7 of the instant application is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7-9, 33, 42, 44-45, 47-48 of the copending US application SN= 10/196732, as evidenced by Maloney DG et al, 1997, Blood, 90(6): 2188-95, of record.

Claims 7-9, 33, 42, 44-45, 47-48 of the copending US application SN= 10/196732 anticipate or would have been obvious over the claim 7 of the instant application.

The combined embodiment of claim 7 and depending claims 8-9, 33, 42, 44-45, 47-48, as directed to a method for treating a human having B-cell lymphoma, wherein the lymphoma is non-Hodgkin's lymphoma, wherein the patient is refractory to treatment with a chimeric anti-CD20 antibody, or rituximab, comprising administering a radiolabeled anti-CD20 antibody, wherein the radiolabeled anti-CD20 antibody is a murine antibody, and wherein the radiolabeled anti-CD20 antibody comprises iodine-131 label, anticipates the claim 7 of the instant application.

The only difference is that the instant claim 7 recites that the subject has CD20 positive B-cell lymphoma, which is however an inherent property of B-cell lymphoma, such as non-Hodgkin's lymphoma, as evidenced by Maloney et al. Maloney et al teach treatment of patients with low-grade non-Hodgkin's lymphoma, using Rituximab (IDEC-C2B8), a chimeric

monoclonal antibody directed against the B-cell specific antigen CD20 expressed on non-Hodgkin's lymphoma.

Thus, although the conflicting claims are not identical, they are not patentably distinct from each other because they relate to the same inventive concept.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SHANON FOLEY can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SHANON FOLEY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600